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KALA-AZAR AS AN ANALOGOUS DISEASE TO MALTA FEVER.

Preliminary Notes of an Investigation and some Discoveries regarding the Nature of the Condition known as Kala-azar.

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Kala-azar has for a number of years been one of the riddles of tropical medicine. There have probably been few diseases so frequently investigated during so short a period in which such varying conclusions have been arrived at by those who have been occupied with the work of investigation.

In 1900 Giles declared the disease to be the result of ankylostomiasis, either by itself, or in some cases complicated with a coincident malarial infection. A few years later Rogers was equally emphatic in his repudiation of the ankylostomal theory of origin. He states, after a lengthy discussion of the whole question: "The disease, then, is a very intense form of malarial fever."

Still more recently, Ross, in his exhaustive and interesting "Report upon the Nature of Kala-azar," appears to insist on the non-malarial nature of the second stage of the disease. It is true that he states, "I think, then, with Rogers, that kala-azar is malarial fever," but this statement is so qualified in the text that he is generally quoted as describing the condition to a peculiar form of post-malarial cachexia. Thus Manson, in his work on "Tropical Diseases," says:—

"Ross . . . considers that kala-azar and a similar condition called kala-dunkh are virtually forms of post-malarial cachexia akin to, if not identical with, similar conditions met with elsewhere in malarial countries."

I do not think that it can be said, however, that either of these conclusions have been accepted in their entirety of recent years by medical men who have had occasion to see much of the disease.

During the past eighteen months I have seen and treated some 400 cases of kala-azar, and I have had the opportunity of watching the gradual invasion of previously healthy coolie lines by an epidemic of this disease.

I have thus had ample material at my disposal for a study of the condition, both from a clinical and epidemiological standpoint. Many cases I have watched from the very beginning, having known them as healthy coolies previous to the contraction of the infection. The careful study of these cases has given me a fairly accurate knowledge of the cause of the disease, and the chief clinical features which present themselves to the observer during the various stages of the affection.

Since I began the study of the disease I have been gradually forced to the following conclusions, based upon the results of clinical, epidemiological, and microscopical observations:—

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(1) Kala-azar is neither malarial fever, benign or malignant; nor is it any form of malarial cachexia or post-malarial cachexia. It may, however, be complicated by a coincident malarial infection.

(2) Kala-azar is a distinct disease, of which the first and second stages as described by Ross, in which an initial attack of irregularly intermittent, remittent or continued fever, followed by recurrences of a similar nature in the first stage, the second stage of nearly continuous fever of a low type, together constitute the whole of one febrile affection of long duration.

When reading up the available literature upon kala-azar, I was struck by the fact that very many of its earliest observers were reported as having expressed the opinion that the condition was either not malarial, or that it was something more than a malarial infection.

The following extracts from Rogers' report upon kala-azar are very strong evidence that the medical men therein quoted had not failed to note the wide divergences between kala-azar and malaria.

Dr. Warburton, Sanitary Commissioner in 1893, writes: " . . . its unequal incidence, where sanitary conditions appear equally bad, the gradual and steady progress downhill unaffected by treatment, the statement that it is slowly but steadily extending up the valley, seem to point to something more than malarial cachexia."

In the sanitary report for 1894, Dr. Stephen, who had succeeded Dr. Warburton, gives the following summary of the opinions of some of the civil surgeons who had seen the disease.

" Surgeon-Major Boruah is of opinion that kala-azar is something more than malarial cachexia.

" Surgeon-Major Campbell is under the impression that the disease is malarial fever, complicated in 75 to 80 per cent. of cases with ankylostomiasis. He, however, is not quite certain that some other cause does not come into play, as later in his letter he states that were a bacteriologist appointed to investigate the condition, he might discover it to be due to some micro-organism, differing from the *Plasmodium malariæ*.

" Mr. McNaught believes that it is a specific disease distinct from malarial fever.

" The medical officers of tea gardens who met at Kokilamukh on October 30th, 1894, after examining persons suffering from kala-azar, brought before them by Drs. Price and Lavertine, of Nowgong, came to the conclusion that the disease was distinct from malarial fever, as they remark that it appears to be entirely unknown in Upper Assam."

Surgeon-Colonel Stephen gives it as his opinion: " From what I have seen of the disease, and from what I have been told of it by those who have had the opportunity of studying it, I am under the impression that although allied to malarial fever, it is probably a separate disease; and as none of the remedies used seem to have had any effect in stopping its ravages, and as it is steadily spreading eastwards up the Assam Valley on both sides of the river, I would recommend that a specialist be appointed to inquire into its cause."

The idea, then, that kala-azar is a non-malarial fever is no new one. It appears that most of the observers whose opinions have been quoted based their doubts as to the malarial nature of the condition upon its well-known epidemic character, and the strong evidence of its communicability.

At that time no one, except perhaps Mr. McNaught, who has had most exceptional opportunities of studying the disease, appears to have questioned the clinical resemblance of kala-azar to ordinary paludism. Indeed, many men have insisted upon the extraordinary likeness which the clinical picture of the disease bore to the type of malarial fever common to the country. This mistake has been largely due to the confusion that has existed for so long regarding the various forms of malarial fever and other febrile affections, whether caused by the presence of the bacillus of Eberth or the *Micrococcus melitensis*.

It is only very recently that the great frequency of typhoid fever among the natives of India was definitely proved, and there still remain a certain number of medical men who doubt the truth of this conclusion on clinical grounds alone. The same may be said in regard to Malta fever, which is probably still regarded as an entirely foreign disease by the bulk of the practitioners of the older school resident in this country. It is only since 1897, when the occurrence of this latter disease in certain parts of India was definitely shown by Wright, Semple, Smith, and others, that medical men have begun to regard it as a possible factor in the causation of some of the atypical sub-continued fevers so common in many parts of India.

It is a matter of common knowledge that the terms " ague " and " remittent fever," still in general use in India as a nomenclature for malarial fevers of all types, have for many years covered a multitude of sins of omission in regard to the correct diagnosis of the febrile diseases prevalent in this country.

Fortunately, recent developments in hæmatology have placed a certain method of diagnosis in the hands of the medical man of the present day, and the result will be an almost complete reclassification of many tropical fevers previously differentiated by clinical features alone.

Quoting Marchiafava and Bignami, we can say: " Hence the progress now made lies essentially not in the increase in the number of pictures of malaria, but in the elimination, guided by the examination of the blood of all those forms which the insufficiency of means for diagnosis has led many authors, and leads even recent writers, to attribute to this infection." And again: " Those clinical types of sub-continued or remittent fever, as one may say, which deviate so far from the common forms of malarial fever in their course, and in their behaviour when treated with the salts of quinine, &c., as, for instance, the sub-continued fever described by Colin, the so-called typho-malarial fevers, Sternberg's adynamic remittent, many of Schellong's remittents, &c., these clinical forms no longer appear in the recent descriptions of those who have taken the examination of the blood as their sure guide."

As I hope to indicate later, the examination of the blood entirely negatives the assertion that malarial infection is the primary cause of kala-azar, but I am anxious first of all to show that on clinical grounds alone we are justified in denying to the malarial para-

site any active part in the production of this disease and its subsequent cachexia.

Clinical Picture of the Disease (Kala-azar).

The disease commences with an attack of high fever, which may be preceded by a rigor or chill, and in some cases vomiting. The fever may be very severe, and varies in type, being intermittent in a few cases, though more frequently remittent or subcontinued in character. It lasts for periods of from two to six weeks, and occasionally longer. During the fever, unless previous anæmia was marked, the spleen and then the liver become enlarged. The fever is followed by a period of apyrexia, during which time the patient appears to improve, but after an interval of varying length a recurrence of the fever takes place. No treatment has yet been successful in preventing these recurrences in the cases of the epidemic form of the disease. Quinine, although it certainly has some slight favourable action, has entirely failed to check the initial pyrexia or to prevent the recurrence of the fever, even when given in doses of 90 gr. in the twenty-four hours during the primary attack and continued throughout the apyrexial period. This has been my experience in a large number of cases. The second attack of fever remains for a more or less indefinite period, and is then followed by another dis-

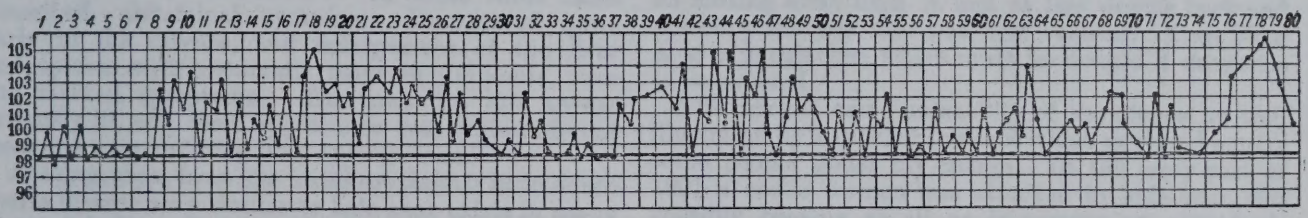

Chart of Early Stages of Kala-Azar.

appearance of the fever, only of a temporary nature, however. Alternating attacks of fever and periods of comparative freedom from pyrexia may continue to take place until at last the patient becomes the subject of a low form of fever, rarely rising above 102°, but remaining persistent in spite of all treatment, often for many months at a time.

As the attacks of fever alluded to above recur, the patient becomes the subject of marked splenic and hepatic enlargement, and may experience considerable pain and tenderness over these organs. Rigors do not generally appear during these secondary attacks, but patients often complain of feeling chilly during the accession of fever. Profuse sweats may often be observed upon remission of the fever, and it is frequently only by the occurrence of these perspirations that a patient is enabled to tell whether he has been suffering from fever.

Pains and aching of the limbs and joints also frequently occur, and have often led to a diagnosis of "rheumatism" on the part of the native medical officers who may be called on to treat the case. Emaciation and anæmia of a mild grade soon becomes noticeable in the subjects of the disease, and, with the increase of the liver and spleen, cause the patient to present a typical appearance. At this stage the swollen abdomen, standing out in marked contrast to the skeleton-like limbs, together with the extraordinary earthy-grey colour of the skin, stamp the patient as the victim of some terribly chronic and debilitating affection. During this period of low fever, which to both patient and medical man often appears never-ending, many minor symptoms occasionally show themselves. Thus marked headache, usually frontal in character, a change in the character of the hair, which loses its pigment and becomes dry and brittle, or may almost wholly fall from the scalp, and the occasional appearance of petechial patches, chiefly about the axillæ, occur in a proportion of cases. Frequent epistaxis and hæmorrhages from the gums are also seen in some cases. The condition of constant low fever, associated with gradual emaciation, enlargement of the spleen, and anæmia, may continue for many months, until some improvement takes place or the patient is carried off by some intercurrent disease. Finally, however, a post-febrile stage may be reached in which the enlargement of the organs often disappears, but the emaciation and anæmia remain until, perhaps, very slowly recovery takes place. More often death results by dysentery, phthisis, pneumonia, or pure asthenia.

It may be remarked that the anæmia, though often severe, never reaches the degree usually seen in marked cases of so-called ankylostomiasis, unless the patient happen to suffer from a severe coincident infection by the ankylostoma.

Death may occur from a sudden access of high fever at any stage of the disease, but at least 90 per cent. of the mortality must be attributed to dysenteric complications, the remaining 10 per cent. resulting from the causes enumerated above.

Epidemiology.

Though the disease has only been described in epidemic form there is little doubt but that it occurs sporadically, and that mild forms of the infection are frequently seen. Medical men in parts of Assam, which are or have been subjected to an invasion of the epidemic, often have occasion to treat cases of obstinate fever, both in natives and Europeans, resisting ordinary doses of quinine, and lasting for periods of many weeks or months. These mild infections, however, are generally vaguely called "remittent fever," and the eventual recovery of the patient is quoted as proof conclusive that the affection was not kala-azar.

Ross, in his report, mentions cases of this nature occurring in Secunderabad, Bangalore, Sigur Ghat, and the Darjeeling Terai; and Captain W. H.

Horrocks, I.M.S., in an interesting paper read before the First Indian Medical Congress of 1894, gives an account of three cases of apparently similar character. He says: "The cases in which the symptoms of enteric (?) fever were associated with continued fever extending over many months are very interesting, and their exact pathology as yet cannot be determined, as they all recovered."

In the case of Lance-corporal H., fever continued for eighty-one days. During the first three weeks his condition strongly resembled an ordinary enteric case. Then the abdominal symptoms disappeared, and he suffered from rheumatic pains, chiefly in the hip joints. The bowels were obstinately constipated, and he gradually became extremely emaciated.

In Surgeon G.'s case the fever continued for sixty-four days. He suffered from abdominal distension, pain in the right iliac fossa, and epistaxis. The bowels were constipated, and the liver and spleen gradually became much enlarged.

In Private C.'s case the fever did not maintain a continued type throughout the disease, but seemed to come on in successive waves during a period of two hundred and fifty days. After the first three weeks he never showed any abdominal symptoms, but the liver and spleen gradually became much enlarged, and he suffered from rheumatic pains in the joints of the lower extremities.

Further on he continues: "In these three cases described, abdominal symptoms disappeared quite early in the disease, and enlargement of the liver and spleen, with rheumatic pains in the joints, were the marked symptoms. The men did not appear seriously ill, and their appearance was quite different from the men suffering from enteric fever."

Judging, then, from the instances there is little doubt that a disease very similar to kala-azar exists in many parts of India, and there is the possibility that it is endemic there, much as Malta fever is endemic in Malta.

Kala-azar as an epidemic appears to have been introduced into Assam as a continuation of an epidemic fever, of a lingering and exceedingly fatal form, which was prevalent in Rungpore during the later sixties and early seventies.

According to Rogers, who has been carefully investigating the history of the disease, it was first mentioned as existing in the Garo Hills about the year 1872, but it did not appear to have made much headway until 1875. The Garos called it "Sirçari disease," or "Sahib's disease," giving as their reason the statement that the condition was unknown in their country until after the British occupation.

From the Garo Hills the disease has gradually spread up the valley of the Brahmaputra upon both sides of the river. It has travelled along the chief lines of communication, and has advanced from point to point without any coincident climatic change to account for an increase of malaria. The most extraordinary feature of the epidemic is the way in which it has attacked the indigenous population, who have been the first to be attacked, and who have probably suffered most severely. These people have been subject to malarial fever for many generations, and have doubtless acquired as marked an immunity to the disease as the natives in West Africa; it is therefore most improbable that they should be the first to feel the effects of an epidemic of malarial fever, and the ones to suffer most markedly. Such a supposition is entirely opposite to the experience of those who have studied malarial fever in other countries than India.

Next to the indigenous population, the oldest residents—time-expired coolies—have suffered most frequently, and from them the disease has been spread to old coolies upon tea gardens. Let me emphasise the fact that it is always the oldest residents that suffer first, although almost anyone exposed to the infection may contract the disease. I have visited a village of Kacharies (one of the indigenous tribes) of Assam which in two years lost 150 people from this disease. The empty houses were to be seen on all sides. On inquiry I learned that only three male adults had been left alive, and the population of the village consisted of these three men, some fourteen women, and a number of children of various ages. On questioning one of the men, he told me that the fever was quite different to the ordinary fever from which they sometimes suffered. That, unlike this fever, it was very severe, and besides lasting for many days, it always returned, until at last the patient died. The Kacharies state that the only way to avoid infection when once it has made its appearance is to keep on moving away from it, and at last double back and reoccupy the site that was first vacated. They liken it to a jungle fire, which must be dodged if danger is to be avoided.

The marked communicability of the disease is well illustrated by a striking incident which occurred among some people under my charge. In the early part of 1901 a coolie woman was attacked by kala-azar, and speedily became so ill as to require an attendant. Her husband, a sirdar, was allowed to remain from work in order to nurse her. After two or three months the woman died, and almost immediately afterwards her husband was attacked by the disease. Soon his condition necessitated a nurse, and a man of the same caste was put to attend him. After two months this attendant contracted the disease. Another man was allowed to act as nurse, but he also took the infection almost immediately. Then a third man was placed in charge of the case, and meanwhile the two former attendants both died. Then the sirdar died also, and within a fortnight the third and last attendant developed the disease, and after a very rapid illness he succumbed to the infection. These five cases occurred among old coolies who had kept good health for many years previously. The five successive cases covered a period of about twelve months.

What is the Nature of the Disease?

A careful examination of the facts at our disposal regarding both the clinical features and the epidemiology of kala-azar appears to me to negative the idea of malarial infection, whether chronic or acute. If we apply the three principles of diagnosis for malaria so clearly laid down by Manson: the clinical, that is, periodicity; the therapeutic, behaviour under quinine treatment; and, lastly, the microscopical examination of the blood—we shall be struck by the

significant fact that by neither of these methods can we arrive at a diagnosis of malaria when dealing with a case of kala-azar.

I propose to apply Manson's three methods in detail, and so I shall therefore first discuss the diagnosis from a clinical aspect.

Periodicity.

If we examine the chart of an early case of kala-azar, we shall probably note the remarkable irregularity of the febrile period. Sometimes the chart may resemble some of the irregular æstivo-autumnal malarial charts, but more frequently it possesses no sort of periodicity in its remissions. Sometimes, however, it shows periodicity, but when it does so it is only quotidian in character. Even then it does not resemble malarial quotidian periodicity so much as it does that seen in acute infective diseases. I have seen cases which exhibited a quotidian rise and fall almost identical with those shown in a chart from a case of infective endocarditis, given in Craig's recent book upon the "Æstivo-Autumnal Malarial Fevers."

In the second stage of kala-azar it is true the fever is usually periodical in character, but here, again, it is of a low type and of such long duration as to be altogether atypical of quotidian malarial fever.

what a remarkable analogy exists between the clinical pictures of Malta fever and kala-azar.

Detailed Comparison between Malta Fever and Kala-azar.

Age of Incidence.—Bruce gives the age of greatest incidence for Malta fever at from 6 years to 30 years. Rogers states that the age-incidence of kala-azar is 58·5 per cent. between 10 and 35 years, and 24·4 per cent. below 40 years. I can confirm Rogers' remark from my own experience. It is chiefly the younger individuals who are attacked by kala-azar. Very young children, however, seem often either to escape or to suffer less severely, although they are by no means exempt from attack.

Duration of the Disease.—Malta fever and kala-azar are the only two febrile diseases at present known in which the pyrexia may remain with but few intermissions for periods extending up to eighteen months. Bruce gives the duration of Malta fever at anything between a few weeks up to one and a half years. Kala-azar may last for two years, but its more common duration is about six months, though mild cases do not last nearly so long. Rogers gives the average from 193 cases at 7·4 months.

Character of the Fever.—According to both Hughes and Bruce, Malta fever tends to exhibit a chart showing a series of waves or undulations. This feature, however, is not constant, for a markedly irregular chart is not uncommon.

In kala-azar there may sometimes be seen an attempt at the formation of long undulations in the pyrexial curve. Often, however, the early temperatures show only marked irregularity. In the second stage there is usually a very regular temperature curve, the daily rise and fall maintaining a monotonous sequence week after week.

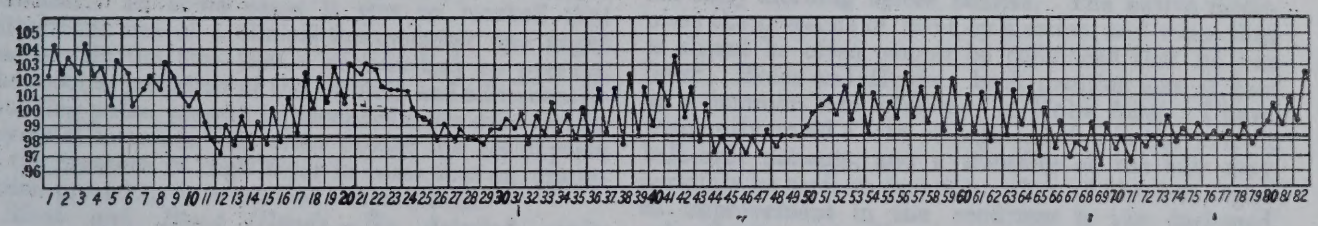

Chart of Case of Malta Fever.

Other Clinical Features of Diagnostic Value.

No doubt the occurrence of such a group of symptoms as fever, anæmia, pigmentation of the skin, enlargement of the spleen and liver, and apparent relapses after recovery, have caused kala-azar to bear a fictitious resemblance to paludism. But before expressing an opinion from these points alone we ought to ask the question, "Whether there is any other condition which exhibits these symptoms also?" A short study of any modern text-book dealing with the diseases of warm climates will satisfactorily answer the question in the affirmative.

In Manson's standard work a reference to p. 206, under the heading "Mediterranean Fever," we find the following definition:—

"Malta fever . . . a disease of indefinite duration . . . is characterised for its more typical form, or rather, made up of a series of febrile attacks, each attack, after lasting one or more weeks, gradually subsiding into a period of absolute or relative apyrexia of several days' or weeks' duration. Each spell of relative apyrexia is followed by a period of fever, which is again succeeded by relative apyrexia."

Further reference to the descriptions of this disease by Hughes, or by Bruce in Davidson's well-known book on the "Diseases of Warm Climates," shows

Comparison of General Symptoms.

Physiognomy.—According to Bruce's description of Malta fever, as it occurs among Europeans, the expression of the face becomes dull, listless, apathetic and anæmic. In long and severe cases the face may become of a dull clay colour. In kala-azar the patient soon shows a typical facies, best described as lethargic. He rapidly becomes anæmic-looking, although on examination his blood may be found with a fair percentage of hæmoglobin. His skin takes on a dull, unpolished, greyish earth-coloured appearance. It is a condition that I have so frequently remarked in conjunction with an enlarged spleen that I have often termed it the "splenic facies."

Alimentary System.—Vomiting and diarrhœa are sometimes reported as occurring in Malta fever, although constipation is one of its marked features. Similar symptoms are not infrequent in cases of kala-azar. Enlargement of the liver is reported as one of the pathological changes present in Malta fever (Bruce and Hughes). In some cases met with in India the enlargement is very marked. In kala-azar the increase in the size of this organ has by some been considered pathognomonic of the disease. In my experience, however, it may often be absent in milder infections. When markedly enlarged it is usually associated with ascites.

Respiratory System.—Epistaxis is common in both Malta fever and kala-azar. Pulmonary complications are not uncommon in Malta fever, a catarrhal condition being frequently seen in conjunction with high fever. In kala-azar pneumonia is a very common complication, and in many cases it appears to precede an attack of the disease. In the latter stages phthisis may supervene and eventually carry off the patient.

Circulatory System. — Palpitation is commonly developed during the courses of both Malta fever and kala-azar. A peculiarity referred to by Bruce as occurring in Malta fever, when the pulse-rate may remain practically normal in the presence of high fever, is one which I have frequently observed in kala-azar. In some cases it was so marked that without the use of a clinical thermometer one might readily gain the idea that a patient had no pyrexia. The peculiar pulsation of the carotids and a frequently-bounding pulse, present in advanced cases even during apyrexial intervals, has often caused the assumption of the presence of high fever in cases that on examination proved to have normal temperatures.

Blood and Blood Glands.—No detailed study appears to have yet been made of the hæmatology of Malta fever. Bruce gives the average number of red cells present at 3,500,000, and states that the leucocytes are usually normal in number. Cabot, Ewing, and Da Costa mention no changes of any importance. Apparently the condition has been neglected by most investigators. In kala-azar Rogers gives the average number of red cells at 2,460,000, and describes a marked decrease in the white elements. I cannot say that I have noticed this lessened number among the leucocytes.

The differential leucocyte count has frequently shown a very marked increase in eosinophiles. A probable explanation is the universal infection of coolies in Assam by the ankylostoma duodenale.

Bruce mentions the fact that pigment is rarely found in the peripheral circulation in cases of Malta fever. Ross found melanin present in 12 out of 26 cases of kala-azar examined by him in Nowgong. I cannot say that I have found it very often, although I have examined the blood of a large number of cases.

A moderate grade of secondary anæmia is generally reported as being commonly present in cases of Malta fever. This corresponds fairly well with what I have found in kala-azar. In cases of this disease, provided the patient is well fed, marked anæmia does not quickly show itself. It is only in cases who from some cause or other have not received a sufficient quantity of nourishing and digestible food that any great degree of anæmia may be found.

The hæmoglobin average of a large number of long-standing cases of the disease, examined by me, worked out at rather over 35 per cent. of Gowers' standard. This figure really represents about 50 per cent. of the normal in natives of Assam.

Enlargement of the spleen is referred to as a constant feature of Malta fever by various observers. It is also given as one of the pathognomonic symptoms of kala-azar. There are, however, many exceptions to both these statements.

Lieutenant E. O. Greig, I.M.S., has reported several cases of Malta fever occurring in the Swat Valley, where no enlargement of spleen or liver were found. On the other hand, increase in the size of these organs is not always present in cases of kala-azar. I have seen several cases in which there was no appreciable enlargement of the spleen, and many others which showed no hepatic enlargement.

Integumentary System.—Profuse perspirations are common to both Malta fever and kala-azar. The nightly-recurring "fever" which many natives, sufferers from the latter disease, complain about is really a recurring night sweat, occurring on the slight remission of the fever which takes place often in the early morning before sunrise. The native recognises the presence of fever by a sweat, and when that is absent he often cannot be convinced that he has fever. Bruce and Hughes both mention loss of hair as a common late symptom in Malta fever. I have frequently noted a loss of pigmentation in the hair of kala-azar patients, and a thinning of the hair may certainly be seen on occasion. One of the first signs of improvement in the condition is the darkened colour and thickened growth of the hair.

Nervous System. — Delirium and headache are common to both diseases in the early stages.

Pain and Swelling of the Joints.—This important symptom of Malta fever is frequently present in cases of kala-azar. Rogers mentions it as being so common as to lead to the admission of cases under the heading of rheumatism. I can confirm this as occurring in a large proportion of cases.

It will be seen from this somewhat lengthy comparison that there is very little to choose between the clinical pictures of these two diseases, and when we take into account the fact that the one description applies to Europeans and the other to natives of India, it will readily be seen what a striking analogy the two conditions present.

We have seen, therefore, that another disease than malaria may exhibit a train of symptoms and produce a condition almost identical with kala-azar, and the existence of such a disease being shown, the force of Ross's arguments against the idea of kala-azar being such a separate entity is entirely turned. How it occurred that the possibility of kala-azar being an epidemic form of Malta fever of a severe type has not presented itself to previous observers I cannot say, but the fact remains that this disease has been reported to have been present in certain parts of India since 1897, and before this, in 1894, Crombie spoke of the possibility of similar conditions being endemic

in this country, although at that time it was supposed that Malta fever proper was only an imported disease.

Evidence is accumulating from day to day to show that so-called Mediterranean fever is present all over the world in tropical and subtropical countries, and recently it has been shown to occur in Assam by Dr. J. A. Hislop and Major Semple, R.A.M.C.

I have also met with a number of cases of the disease, and as soon as I can arrange to apply the agglutination or sedimentation test in routine practice I have little doubt but that I shall be able to show that a large proportion of cases of fever met with in this part of Assam are of a similar nature.

As Ross has pointed out, the chief objections to the malarial theory of kala-azar are: (1) High death-rate and the intractability of the disease to quinine; (2) the absence of parasites and pigment and the existence of low fever in the later stages; and (3) its communicability.

As you will no doubt observe, the weight of these objections is increased fourfold with the discovery of another disease which presents such a marked similarity to kala-azar and to which only the first of these objections can be said to apply. In regard to point 3 I should like to direct your attention to the fact that in kala-azar, as all those who are familiar with the disease will agree, persons well advanced in the second stage of the disease are capable of conveying the infection to fresh localities, and forming new foci of infection. In fact, it is these people who have done most to spread the disease. Yet it is precisely, according to Ross, people who are in the second stage of the disease who should prove absolutely incapable of conveying the infection were it malarial, because as he has shown, they do not in that stage harbour any malarial parasites.

This appears to me to be a fatal objection to the malarial theory of origin, apart from any other evidence against the idea.

Another objection which I should like to urge against the theory of kala-azar being a post-malarial condition is the lack of any recent confirmatory evidence of the existence of such a fever as the *fièvre symptomatique* of Kelsch and Keiner, following upon a malarial infection. The only authorities who appear to mention such a condition are those quoted by Ross. Vandyke Carter's paper in which he mentions such a condition was published in 1887, the same year in which the *Micrococcus melitensis* was discovered. The work of Kelsch and Keiner appeared in 1889, and it is scarcely possible that these observers should have been able to take into much account in these researches the existence of this new factor in the etiology of continued fevers. It appears to me very probable that the fever described by them may, on further investigation, be found to be of non-malarial origin, but with a similar causation to kala-azar. Mannaberg distinctly states that he had never met with this fever, which, as he says, must be very rare.

The Therapeutic Method of Diagnosis.

Before passing on to the hæmatology of kala-azar I should like to call attention to the behaviour of the disease to treatment by the salts of quinine.

Practically all observers are agreed that quinine exerts but little influence in checking or controlling an attack of kala-azar. In some cases I have certainly seen an improvement in the condition of a patient while taking full doses of the drug, but I am inclined to think that this improvement was probably due to the fact that the patient was at the same time the subject of a coincident malarial infection. This idea is borne out by the experience that quinine appears to act most beneficially in those cases of the disease which occur among the most recent arrivals in Assam and who are probably the most susceptible to malarial infection. In the bulk of cases among old coolies, or among their children, born in the district, quinine exercises absolutely no beneficial influence. If given in very large doses it certainly has an effect in restraining the fever, but does not appear to exert any curative action. In the case of a woman now recovering from the disease, however, doses varying from 30 to 50 grs. per diem have been administered for ten months. Her fever, which continued almost the whole time, has now ceased, but any attempt at stopping the daily dose of quinine is quickly followed by a rise in temperature. Until quite recently, before I became absolutely convinced of the non-malarial nature of the condition, I have been in the habit of administering exceedingly large doses of quinine in the early stages of the disease, with a view to preventing the onset of the second stage of what I then supposed to be a malarial condition. To this end I have given quinine in repeated doses of from 30 to 60 grs. at one time, by the mouth, or 30 grs. intramuscularly by means of a Pravaz syringe. I used these doses after finding ordinary doses of no effect. In some few cases a temporary reduction of temperature took place. A peculiarity of many of these cases appeared to be their insusceptibility to the action of quinine. Cinchonism, except of a most temporary character, was never produced even after the heaviest doses. This drug can only be considered of use as a diagnostic agent, in cases of kala-azar, in a negative sense (as regards the malarial theory of its origin).

The Microscopic Examination of the Blood.

I cannot pretend to do justice to the hæmatology of kala-azar in this paper, but I hope to be able to indicate the true nature of the condition, as well as to show that the theory of malarial origin of the disease, is quite untenable.

Ross has shown in his report in how few instances of recognised kala-azar it was possible to find either malarial parasites or melanin—the evidence of their recent presence.

He himself recognises this as being one of the strongest objections to his theory. I do not need to add anything to what he has said beyond stating that to my knowledge several accepted authorities upon malaria have been unable to find any sign of malarial infection by the examination of films of blood from early cases of the disease. I have examined a very large number of cases personally, and only once have I found a living parasite in the peripheral circulation of a case, and in two other cases I have observed malignant malarial parasites (whether tertian or quotidian I cannot say) present in the splenic blood. I have likewise only once found a crescent body in

splenic blood taken from a case of kala-azar. In very few cases have I have been able to observe pigment in the peripheral blood, neither have I found pigmented leucocytes except on one or two occasions.

The differential leucocyte count of a small series of cases, which I examined, gave :—

Polymorphonuclear neutrophiles	..	48 per cent.
Lymphocytes (small)	..	24·0 ,, ,,
Eosinophiles	..	12·7 ,, ,,
Large mononuclear	..	14 ,, ,,

I also observed a few normoblasts in several of the specimens. The large percentage of eosinophile cells noted is accounted for by the universal infection of all coolies in this part of Assam by ankylostoma in varying numbers. I have occasionally seen a very marked lymphocytosis in cases of kala-azar, even when no apparent cause existed to account for the increase.

The red cells do not appear to suffer much change in the absence of any other condition calculated to produce anæmia. Sometimes, as already mentioned, a few nucleated red cells may be seen. Poikilocytosis is uncommon, and polychromatophilia is rarely noted until a very late stage of the disease.

Blood-plates are usually very much increased, and appear to take on some change. In fresh films stained by Nakanishi's method, they often exhibit distinct spots of darker staining reaction. These are often so large as to be countable by means of an eighth-inch objective. These spots vary in number from one to five, and owing to the marked molecular movement of the bodies containing them, they led me at first to consider the possibility of their being organisms of some kind. In films dried and stained in the usual way they do not appear to exhibit any peculiarity, and their great number, together with the absence of intracorpuscular bodies at the same time, negatives the idea of their being the spores of malarial parasites. The great increase in the blood-plates is perhaps of some little diagnostic importance, because it appears in the pyrexial stage. Cabot, Ewing, and Da Costa state that blood-plates are decreased in malaria and most febrile affections, the exceptions being bubonic plague, measles, erysipelas, and scarlet fever.

To sum up briefly, the hæmatology of kala-azar lends no support to the malarial theory of origin, while it corresponds to the little at present known of the blood conditions in Malta fever. The application of the three methods of diagnosis recommended in cases of suspected malarial fever has shown that kala-azar fails to answer (1) the clinical test; (2) the therapeutic test; and, lastly, (3) the blood examination test. It therefore appears to me no longer possible to consider the question of malaria as a factor in the production of the disease.

I have put forward another theory which appears to me to agree with all the known facts about kala-azar, and to explain some of the pecularities of the infection. We will now see what direct evidence can be shown to prove the correctness of my idea. Clinically, as I think every one will admit, the two diseases appear to resemble one another very strongly.

If we refer to any modern text-book dealing with Malta fever, we may see that most authorities agree in the statement that the diagnosis of Malta fever is to be made by the serum reaction of the case to cultures of the *Micrococcus melitensis*. Hughes states that the disease may be diagnosed from enteric fever, paludism, phthisis, liver or pelvic abscess, empyema, and other suppurating diseases, &c., by the reaction of the blood to cultures of the micrococcus of Malta fever, by the absence of the local and special symptoms of these diseases, and the absence of malarial parasites in the blood. He further states "that the serum reaction is often the only reliable sign," as the disease frequently simulates other conditions.

Let us see, then, how the blood of kala-azar patients reacts to the cultures of the *Micrococcus melitensis*.

About six weeks back, while examining the spleen pulp from a fatal case of kala-azar, I was surprised to find a number of micrococci present among the splenic cells and tissue. I was at once struck with the possibility of the condition being of micrococcal origin, and knowing that Malta fever was certainly present in the district, I certainly determined to have the matter cleared up.

Accordingly I sent two batches of blood specimens to Major R. Semple, R.A.M.C., Director of the Pasteur Institute, Kasauli, who has been most kind in examining them for me, for the reaction with cultures of the *Micrococcus melitensis*.

The results of these examinations are shown in the annexed table. Taken in conjunction with the finding of a micrococcus in the spleens of two cases of kala-azar, I consider the result of the serum test as absolutely conclusive.

Table of Reactions of Blood (9 Kala-azar and 3 others) to Cultures of Micrococcus Melitensis.

Cases	10 Dilutions	20 Dilutions	40 Dilutions	Remarks
1*	Complete	Complete	Complete	—
2*	Nil	Nil	Nil	—
3	Nil	Nil	Nil	Died
4	Complete	Complete	Complete	—
5	—	Partial	Nil	Died
6*	Complete	Complete	Complete	Died (dysentery)
7	Complete	Complete	Complete	—
8	Complete	Complete	Complete	—
9	Feeble	Feeble	Nil	Died
10	Complete	Complete	Partial	Died
11	Complete	Complete	Nil	Died
12	Complete	Complete	Complete	—

(Nos. 1 to 6 were also examined for reactions to cultures of typhoid, but gave no reaction.)

* Of these cases, Nos. 1, 2 and 6 had not been diagnosed as cases of kala-azar, although there was a marked resemblance to the disease. They had not occurred, however, in a garden infected by the disease, although within one mile cases were common enough. No. 1 recovered; No. 2 was very severely ill, and is still getting fever; No. 6 was not very ill, but died shortly after her blood was examined from severe dysenteric symptoms. All the remaining cases were known to be kala-azar. Of these No. 3 was a very severe case, his temperature ranging between 103° and 105° for nearly three months, with hardly a break. Of the other cases, Nos. 5, 9, 10 and 11 have all succumbed to the disease, the two latter ones within fourteen days of the examination of their blood. These figures support very strongly the conclusions arrived at by Birt and Lamb (*Lancet*, September 9th, 1899). The 9 cases of kala-azar were none of them picked specially. They were taken from among a number of cases of the disease in a line which has become infected during the past fourteen months, the population of which has been under my observation since January, 1901.

Evidently, whatever else it may be, kala-azar is essentially Malta fever. No doubt mixed infections, or rather coincident infections by malaria and dysentery, are common, but the primary condition is the one produced by the micrococcus to which I have referred. In this paper I cannot do more than point to this discovery. The bacteriological and experimental confirmation has not yet been attempted, and must be left to a future occasion.

All that remains for us to discuss at present are one or two points which will be raised by the putting forward of this new theory regarding kala-azar. It may be said that the death-rate in Malta fever is a low one, a fact which does not correspond with what we know of kala-azar. But we must remember that the death-rate for malaria is generally given as being no higher than 2 per cent., exactly the same figure that is given by Hughes and Bruce for Malta fever. Also all that Ross says regarding the question of death-rate when comparing the mortality of kala-azar with malaria applies with equal force to Malta fever.

A quotation from Hughes' description of Malta fever in Allchin's "Manual of Medicine," appears to me to explain very clearly the probable cause of the frightful mortality met with in kala-azar. Under the heading "Prognosis," Hughes remarks:—

"Favourable as regards life . . . . but most unfavourable as regards length of the attack, and consequent interference with livelihood."

The interference with livelihood is, as every one familiar with the conditions of life prevailing in India will admit, one of the most potent causes of increased mortality in any and all the diseases present in that country. Thus it is that we see a terminal form of dysentery complicating all debilitating diseases among the native population, and being directly responsible for nine-tenths of the deaths from these diseases.

Before concluding, it is necessary to ask the question, "How did this disease — kala-azar — arise?" Rogers, in his discussion of this problem, has pointed out the occurrence of epidemics of fever of a somewhat similar character to kala-azar, which took place some forty to fifty years ago in North-east Bengal, in the districts of Burdwan and Rungpore. Is it possible that Malta fever was then a new disease, introduced into India for the first time, perhaps, among the British troops who were poured into the country at the time of the Mutiny? Many of these men had seen service in Malta, Gibraltar, or other parts of the Mediterranean; and, as we know, the infection of Malta fever is a most lasting and chronic one, and might easily outlive a voyage round Africa. The introduction of the disease in this way would account for its extreme virulence. We are all aware that frequently diseases introduced for the first time among people totally unacquainted with them take on immediately the characters of an epidemic, and appear to increase in virulence. And in the case of Malta fever, the argument used by Rogers to explain the increased virulence of kala-azar has a force which its application to the malarial theory destroys. We know that many bacteria increase in virulence by being passed through susceptible individuals. We do not know that this is the case with the protozoal form of parasites.

We can easily imagine, then, how this disease, introduced, perhaps, some forty odd years ago, has gradually been extending over the country, first as a slowly-moving epidemic, and then becoming endemic, just as malaria, cholera, and dysentery.

This theory serves to explain certain points which have hitherto remained as marked exceptions to general ideas regarding malaria. For instance, the fact that the indigenous population of Assam should be the one to suffer most severely from the disease is quite at variance with our knowledge of malarial incidence. Had malaria not existed in Assam before the occurrence of kala-azar we might have understood it; but now we see that, though probably immune to malaria, the Assamese and Kacharies were fatally liable to contract this new disease, and little able to resist it. Passing, therefore, through numbers of susceptible persons, the disease has become aggravated and its effects more marked, as evidenced in the enormous enlargement of the liver and spleen, and the increased mortality.

The reading of the riddle of kala-azar has opened up a wide field for further investigation. At present we are ignorant of the mode of spread of Malta fever, whether through the air, by means of water or food, or by the bites of suctorial insects. We are also ignorant of any remedy for this disease, whose distribution appears to be as wide as that of malaria itself. There is probably no more promising field of research open to those interested in the problems of preventive medicine than the discovery of the means by which the infection of Malta fever is communicated, and the production of some serum or antitoxin, as a curative or prophylactic agent, against this disease.

In conclusion, I wish to mention my indebtedness to Major R. Semple, R.A.M.C., for having so kindly aided me by examining samples of blood—a part of the work for which my inability to obtain the necessary cultures of the *Micrococcus melitensis* has obliged me to seek some assistance in this investigation.

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